SMAD4 gene

SMAD family member 4

Normal Function

The *SMAD4* gene provides instructions for making a protein involved in transmitting chemical signals from the cell surface to the nucleus. This signaling pathway, called the transforming growth factor beta (TGF-β) pathway, allows the environment outside the cell to affect how the cell produces other proteins. The signaling process begins when a TGF-β protein attaches (binds) to a receptor on the cell surface, which activates a group of related SMAD proteins. The SMAD proteins bind to the SMAD4 protein and form a protein complex, which then moves to the cell nucleus. In the nucleus, the SMAD protein complex binds to specific areas of DNA where it controls the activity of particular genes and regulates cell growth and division (proliferation).

By controlling gene activity and regulating cell proliferation, the SMAD4 protein serves both as a transcription factor and as a tumor suppressor. Transcription factors help control the activity of particular genes, and tumor suppressors keep cells from growing and dividing too fast or in an uncontrolled way.

Health Conditions Related to Genetic Changes

cholangiocarcinoma

hereditary hemorrhagic telangiectasia

At least five mutations in the *SMAD4* gene have been found to cause a form of hereditary hemorrhagic telangiectasia called juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome. People with this disorder have the blood vessel problems associated with hereditary hemorrhagic telangiectasia as well as an increased risk of developing intestinal growths (polyps) at an early age; the polyps may become cancerous.

SMAD4 gene mutations that cause this disorder affect the TGF-β signaling pathway. Disruption of this pathway may interfere with both the tumor suppressor function of the SMAD4 protein and the appropriate development of the boundaries between veins and arteries, resulting in the signs and symptoms of juvenile polyposis/ hereditary hemorrhagic telangiectasia syndrome.

juvenile polyposis syndrome

More than 60 mutations in the *SMAD4* gene have been found to cause juvenile polyposis syndrome, a disorder characterized by multiple noncancerous (benign) growths called juvenile polyps. Most *SMAD4* gene mutations that cause juvenile polyposis syndrome result in the production of an abnormally short, nonfunctional protein. A lack of functional SMAD4 protein prevents binding to other SMAD proteins and interferes with the transmission of chemical signals from the cell surface to the nucleus. The SMAD protein complex is not activated and cannot be transported to the nucleus, where it is needed to regulate cell proliferation and the activity of certain genes. This unregulated cell growth can lead to polyp formation in people with juvenile polyposis syndrome.

Myhre syndrome

At least three mutations in the *SMAD4* gene have been identified in people with Myhre syndrome, a condition with features including intellectual disability, short stature, and hearing loss. Each of these mutations affects the protein building block (amino acid) isoleucine at protein position 500 by replacing it with a different amino acid. Some researchers believe that the *SMAD4* gene mutations that cause Myhre syndrome impair the ability of the SMAD4 protein to bind properly with the other SMAD proteins and other proteins involved in the signaling pathway. Other studies have suggested that these mutations result in an abnormally stable SMAD4 protein that remains active in the cell longer. Changes in SMAD4 binding or availability may result in abnormal signaling in many cell types, which affects development of many body systems and leads to the signs and symptoms of Myhre syndrome.

cancers

People with mutations in the *SMAD4* gene appear to have an increased risk of developing various cancers. Some of these gene mutations are inherited, while others are acquired during a person's lifetime. Such acquired (somatic) mutations are present only in certain cells. Cells with mutations in the *SMAD4* gene, whether inherited or somatic, may proliferate out of control and result in a tumor, often in the colon or pancreas.

other disorders

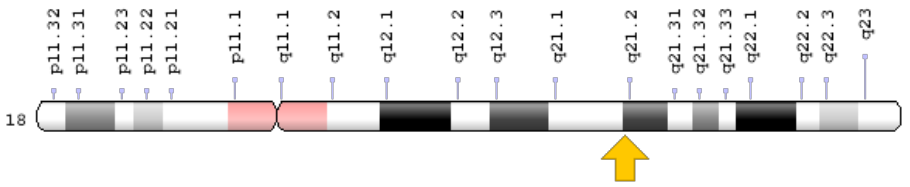
SMAD4 gene mutations have also been identified in a small number of individuals with juvenile polyposis and blood vessel abnormalities other than hereditary hemorrhagic telangiectasia. These abnormalities include weakening and stretching (dilation) of the aorta, which is the large blood vessel that distributes blood from the heart to the rest of the body. Aortic dilation may lead to a bulge in the blood vessel wall (an aneurysm), or may cause the aortic valve to leak, which can result in a sudden tearing of the layers in the aorta wall (aortic dissection). Aortic aneurysm and dissection can be life-threatening. Impaired functioning of the mitral valve, which

connects two of the four chambers of the heart, has also been seen in combination with juvenile polyposis caused by *SMAD4* gene mutations.

Chromosomal Location

Cytogenetic Location: 18q21.2, which is the long (q) arm of chromosome 18 at position 21.2

Molecular Location: base pairs 51,030,213 to 51,085,042 on chromosome 18 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- DPC4
- JIP
- MAD (mothers against decapentaplegic, Drosophila) homolog 4
- MAD, mothers against decapentaplegic homolog 4
- MAD, mothers against decapentaplegic homolog 4 (Drosophila)
- MADH4
- Mothers against decapentaplegic, Drosophila, homolog of, 4
- SMAD, mothers against DPP homolog 4 (Drosophila)
- SMAD4_HUMAN

Additional Information & Resources

Educational Resources

- American Medical Association and National Coalition for Health Professional Education in Genetics: Understand the Basics of Genetic Testing for Hereditary Colorectal Cancer
  http://www.nchpeg.org/documents/crc/Basics%20of%20genetic%20testing.pdf
- Cancer Medicine (sixth edition, 2003): Familial Juvenile Polyposis Coli
  https://www.ncbi.nlm.nih.gov/books/NBK12959/#A4571

- Developmental Biology (sixth edition, 2000): The Smad Pathway Activated by TGF-β Superfamily Ligands
  https://www.ncbi.nlm.nih.gov/books/NBK10043/figure/A1057/
- Genomes (second edition, 2002): SMAD Signaling in Vertebrates
  https://www.ncbi.nlm.nih.gov/books/NBK21127/box/A7928/#A7929
- Molecular Cell Biology (fourth edition, 2000): Mutations Causing Loss of Cell-Cycle Control.
  https://www.ncbi.nlm.nih.gov/books/NBK21526/

GeneReviews

- Hereditary Hemorrhagic Telangiectasia
  https://www.ncbi.nlm.nih.gov/books/NBK1351
- Juvenile Polyposis Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1469

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28SMAD4%5BTIAB%5D%29+OR+%28MADH4%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4
  http://omim.org/entry/600993

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/SMAD4ID371.html
- Cancer Genome Anatomy Project
  https://cgap.nci.nih.gov/Genes/GeneInfo?ORG=Hs&CID=75862
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SMAD4%5Bgene%5D
- HGNC Gene Family: SMAD family
  http://www.genenames.org/cgi-bin/genefamilies/set/750
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=6770

- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4089
- UniProt
  http://www.uniprot.org/uniprot/Q13485

Sources for This Summary

- Andrabi S, Bekheirnia MR, Robbins-Furman P, Lewis RA, Prior TW, Potocki L. SMAD4 mutation segregating in a family with juvenile polyposis, aortopathy, and mitral valve dysfunction. Am J Med Genet A. 2011 May;155A(5):1165-9. doi: 10.1002/ajmg.a.33968. Epub 2011 Apr 4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21465659
- Aretz S, Stienen D, Uhlhaas S, Stolte M, Entius MM, Loff S, Back W, Kaufmann A, Keller KM, Blaas SH, Siebert R, Vogt S, Spranger S, Holinski-Feder E, Sunde L, Propping P, Friedl W. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007 Nov;44(11):702-9. Epub 2007 Sep 14.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17873119
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752176/
- Calva-Cerqueira D, Chinnathambi S, Pechman B, Bair J, Larsen-Haidle J, Howe JR. The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet. 2009 Jan;75(1):79-85. doi: 10.1111/j.1399-0004.2008.01091.x. Epub 2008 Sep 24.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18823382
- Cancer Genome Anatomy Project
  https://cgap.nci.nih.gov/Genes/GeneInfo?ORG=Hs&CID=75862
- Caputo V, Cianetti L, Niceta M, Carta C, Ciolfi A, Bocchinfuso G, Carrani E, Dentici ML, Biamino E, Belligni E, Garavelli L, Boccone L, Melis D, Andria G, Gelb BD, Stella L, Silengo M, Dallapiccola B, Tartaglia M. A restricted spectrum of mutations in the SMAD4 tumor-suppressor gene underlies Myhre syndrome. Am J Hum Genet. 2012 Jan 13;90(1):161-9. doi: 10.1016/j.ajhg.2011.12.011.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22243968
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257749/
- Chow E, Macrae F. A review of juvenile polyposis syndrome. J Gastroenterol Hepatol. 2005 Nov; 20(11):1634-40. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16246179
- Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet. 2004 Mar 13; 363(9412):852-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15031030
- Howe JR, Sayed MG, Ahmed AF, Ringold J, Larsen-Haidle J, Merg A, Mitros FA, Vaccaro CA, Petersen GM, Giardiello FM, Tinley ST, Aaltonen LA, Lynch HT. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. J Med Genet. 2004 Jul;41(7):484-91.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15235019
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1735829/

- Howe JR, Shellnut J, Wagner B, Ringold JC, Sayed MG, Ahmed AF, Lynch PM, Amos CI, Sistonen P, Aaltonen LA. Common deletion of SMAD4 in juvenile polyposis is a mutational hotspot. Am J Hum Genet. 2002 May;70(5):1357-62. Epub 2002 Mar 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11920286
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC447611/
- Le Goff C, Mahaut C, Abhyankar A, Le Goff W, Serre V, Afenjar A, Destrée A, di Rocco M, Héron D, Jacquemont S, Marlin S, Simon M, Tolmie J, Verloes A, Casanova JL, Munnich A, Cormier-Daire V. Mutations at a single codon in Mad homology 2 domain of SMAD4 cause Myhre syndrome. Nat Genet. 2011 Dec 11;44(1):85-8. doi: 10.1038/ng.1016.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22158539
- Lindor NM, Gunawardena SR, Thibodeau SN. Mutations of SMAD4 account for both LAPS and Myhre syndromes. Am J Med Genet A. 2012 Jun;158A(6):1520-1. doi: 10.1002/ajmg.a.35374. Epub 2012 May 14.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22585601
- OMIM: MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4
  http://omim.org/entry/600993
- Merg A, Howe JR. Genetic conditions associated with intestinal juvenile polyps. Am J Med Genet C Semin Med Genet. 2004 Aug 15;129C(1):44-55. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15264272
- Pyatt RE, Pilarski R, Prior TW. Mutation screening in juvenile polyposis syndrome. J Mol Diagn. 2006 Feb;8(1):84-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16436638
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1867574/
- Teekakirikul P, Milewicz DM, Miller DT, Lacro RV, Regalado ES, Rosales AM, Ryan DP, Toler TL, Lin AE. Thoracic aortic disease in two patients with juvenile polyposis syndrome and SMAD4 mutations. Am J Med Genet A. 2013 Jan;161A(1):185-91. doi: 10.1002/ajmg.a.35659. Epub 2012 Dec 13.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23239472
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535513/
- Woodford-Richens KL, Rowan AJ, Poulsom R, Bevan S, Salovaara R, Aaltonen LA, Houlston RS, Wright NA, Tomlinson IP. Comprehensive analysis of SMAD4 mutations and protein expression in juvenile polyposis: evidence for a distinct genetic pathway and polyp morphology in SMAD4 mutation carriers. Am J Pathol. 2001 Oct;159(4):1293-300.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11583957
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1850516/

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